Toxicology and Potential Health Risk of Chemicals that May Be Encountered by Workers Using Forest Vegetation Management Options

PART IV: RISK TO WORKERS USING GLYPHOSATE FORMULATIONS

Forest Practices Branch
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Abstract

Glyphosate, as the isopropylamine (IPA) salt, is the active herbicide in the formulation Vision®, which is the registered name for forestry uses in Canada. It is identical to the agricultural and industrial formulation Roundup®. Vision® and Roundup® formulations contain 41% glyphosate IPA salt (or 35.6% glyphosate acid), 15% surfactant, and water. The surfactant in Vision® is of a type that is common to cosmetics and household products. Its toxicity is well understood and is quite limited.

Absorption of glyphosate from the digestive tract is inefficient. Absorption across the skin is also very slow. Between 0.5 and 2% of glyphosate applied to human skin will be absorbed in 24 hours if not washed off. Washing with water or soap and water has been found to remove almost all of the applied herbicide. Virtually all glyphosate absorbed into the circulation is excreted unchanged by the kidneys in a few days. Glyphosate is not detectable in eggs, milk or meat after dietary treatment of livestock.

The toxicity of glyphosate is limited. Glyphosate and its formulations have no specific target in animals that can serve as a basis for systemic or organ based toxicity. Its action in plants is on a specific biochemical pathway for aromatic amino acid synthesis that does not exist in animals. Glyphosate has no effect on reproduction or fertility, and does not cause birth defects, genetic effects such as mutation, or cancer. The formulation has low skin irritancy and does not cause allergic sensitization.

The amount of glyphosate absorbed by forest herbicide applicators is very low, with safety factors in excess of 5000. After an application has dried, potential for exposure of workers or others entering a treated area is still lower or nonexistent.

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Foreword

Vegetation management is an important reforestation activity for controlling competing vegetation or brush encroachment of young tree seedlings. The activity is necessary to get tree seedlings to free-growing status in most new forest sites established in areas that have been harvested or denuded by wildfire, insects and disease.

There are a number of options for managing forest vegetation. The treatment options include prescribed fire, herbicides, manual removal with hand and power tools (e.g., girdling and slashing tools, chain saws and brush saws), placement of mulch mats, mechanical techniques with heavy machinery, and biological methods. The use of livestock (e.g., sheep) is currently the common biological control technique employed in reforestation areas in British Columbia. Biological methods with insects or specific pathogens is used on forest rangelands for noxious weed control but not commonly used for vegetation control in young forest stands.

The selection of a treatment option involves a decision-making process based on integrated vegetation management concepts that include evaluation of the need for treatment, consideration of all the approved treatment methods and choosing the most appropriate treatment method, monitoring and evaluation. Factors considered in selecting a particular method are the ability of the method to meet the required reforestation objectives, the impact of the treatment at the specific site on human safety and the environment (e.g., recreational resources, fish and wildlife and their habitat, range resources and water supply), as well as the economics of the treatment.

This publication is one of a series of papers that evaluates the potential health effects on forest workers using the commonly employed methods of vegetation control. Other papers in the series are listed at the end of this paper. The emphasis is on risks associated with exposure to chemicals during the use of two most important methods for controlling competing vegetation in regenerated (natural or planted) forest areas. These methods are the use of herbicides and manual removal or control with handheld-motorized (power) equipment.

The herbicides discussed are those that have been commonly used in forestry in Canada. The database on health effects of herbicides is extensive and permits reliable estimates of risk. For components of chain saw exhaust and fuels, there is also voluminous background of toxicological information, but exposure data in forestry is limited. Nonetheless, there is enough information to develop preliminary assessments of potential health effects. While there appears to be a high incidence of physical injury associated with manual methods of brush control, there is virtually no validated data on which to base estimates of risk. The existing data are those of workers compensation boards and insurance companies but such data are generally difficult to obtain or are not specifically enough to characterize the kind of activity that leads to injury.

The information in these reports should provide the basis for important decisions about the way vegetation management in forestry should be carried out, and the use of some forestry activities as a source of assisted employment.

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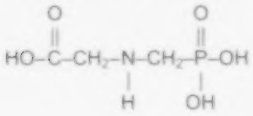
Introduction

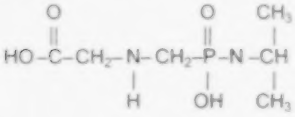
Glyphosate, as the isopropylamine (IPA) salt, is the active herbicide in the formulation Vision®, which is the registered name for forestry uses in Canada. Vision is identical to the agricultural and industrial formulation Roundup®. Forza® and Vantage Forestry®) are new formulations of glyphosate for forestry use in Canada. In this report the formulation names used in reference to a given study reflect the time or context of the research.

The structures of glyphosate (A), the isopropylamine salt of glyphosate (B), and the microbial metabolite aminomethyl phosphonic acid (AMPA) (C) are:

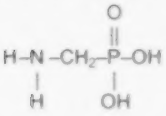
A. Structural formula of glyphosate acid:



B. Structural formula of isopropylamine salt of glyphosate:



C. Structural formula of AMPA (aminomethyl phosphonic acid:



The IPA salt of glyphosate is completely soluble in water. Glyphosate itself is only slightly soluble in water and is not soluble in other solvents, such as benzene or acetone. Glyphosate and its IPA salt have very low vapour pressures and therefore have practically no tendency to evaporate.

Vision® contains 41% glyphosate IPA salt (35.6% glyphosate acid), 15.4% surfactant and 41.6% water. The formulation usually includes organic acids closely related to glyphosate to the extent of about 1.5% and 0.5% excess isopropylamine. The surfactant and water are considered inert ingredients (non-pesticidal substances). Water is the solvent carrying the active ingredient; the surfactant lowers the surface tension of water so the dilute formulation will spread on leaves to be better absorbed. There are no other components of the formulation. The nature of the surfactant and its potential impacts is discussed later. Early production of the formulation contained 1,4-dioxane as a contaminant. It is no longer detectable.

The bulk of data necessary for registration of glyphosate herbicides has been developed in studies conducted or commissioned by the registrant and audited by Health Canada and Agriculture Canada, the Environmental Protection Agency in the United States (USEPA) and pertinent agencies internationally, including World Health Organization (WHO). The database is considered to be complete. While the data for registration is proprietary and confidential, it has been made available under confidentiality agreements to public agencies and other qualified reviewers for the purpose of meeting requirements of environmental impact statements and their background statements, health advisories, registration reviews and other documents.

The material reviewed in those documents for this report is not specifically referenced for each item of information, but the review sources are listed at the end of the reference list. The entire body of data necessary for registration has been reviewed in the USEPA Reregistration Eligibility Decision Document for glyphosate (USEPA, 1993) and summarized by Agriculture Canada (1992). The World Health Organization Environmental Health Criteria 159 (WHO, 1994) reviews data existing at that time. All are public documents. The US Forest Service (USFS) commissioned a risk assessment for glyphosate formulations (Syracuse Environmental Research Associates/Syracuse

Research Corporation, 1996). Two very thorough independent reviews have recently been published, including both registration data and that published in the open literature. Giesy et al (2000) have evaluated the ecological risks associated with use of glyphosate formulations, and Williams et al (2000) have prepared an assessment of risks to humans.

Pertinent research on glyphosate or its formulations that has been published in the open literature is specifically referenced. Published studies of glyphosate outside the registration process are relatively few, however, because there has been little interest in the toxicology of glyphosate or its formulations. There are a number of reasons for the lack of independent research beyond regulatory needs. The most important is that glyphosate is simply not toxicologically interesting.

There are no mysteries about biological interactions of glyphosate that would prompt industrial, academic or federal research. It has no specific target in animals that can serve as a basis for systemic or organ based toxicity. Its action in plants is on a specific biochemical pathway for aromatic amino acid synthesis that does not exist in animals at any level. It has no detectable effect on reproduction or development, it is considered to have no carcinogenic or other genetic activity, it is poorly absorbed and rapidly excreted.

For reasons that are not entirely clear, glyphosate and its formulations are targets of unusual hostile activism claiming a spectrum of serious adverse impacts. These assertions are not supported by valid data. Even some of the truly dangerous insecticides have not had the kind of public attention that some individuals and groups have devoted to glyphosate formulations. These assertions pass from hand to hand and emerge in almost every public discussion of herbicides.

There have also been several reports published in the scientific literature that claim to show adverse effects, but in which the presented data either are not consistent with the claims, or there are flaws in the work that are serious enough to diminish the credibility of the research. The papers also raise general scientific concern because the editorial appraisal and peer review have not been adequate. While requirements for basic data on environmental behaviour and effects of the herbicide have been fulfilled, there is a wide range of environmental conditions that might affect the behaviour of the compound and its effect on crops and plant communities. Consequently, studies of direct and indirect impacts of glyphosate formulations on forest, cropland and stream biota continue to appear because any herbicide has potential to cause changes in habitat, and aquatic species are inherently sensitive to surface active materials. Environmental behaviour is also a determinant of human exposure. Interactions in the environment influence efficacy of a herbicide, and there is a need to study ways to lower the effective application rates.

It will be useful if readers have read the paper discussing the general principles by which health effects of chemicals are judged. A description of the testing process used to evaluate pesticides for registration may be found in Title 2 in this series.

Behaviour of Glyphosate in the Body: Absorption, Metabolism, Storage in Tissues and Excretion

Absorption of glyphosate from the digestive tract is not complete. A summary of several studies in rats indicates that 65-85% of oral intake appears in the faeces (Williams et al, 2000). It appears that efficiency of absorption may decrease as dosage is lowered, but there is insufficient information at the very low doses typical of occupational or environmental exposure.

Absorption across the skin is very slow. A study of monkeys in which glyphosate was held in place on the skin for seven days indicated that

after application of 25 micrograms glyphosate/square centimetre over an area of 20 square centimetres, excretion in the urine averaged 0.8% of the applied amount. At a ten fold higher dose the absorption was 2.2% (Wester et al, 1991). This treatment rate may be compared to the deposition rate of about 20 micrograms per square centimetre that would result from a typical 2 kg/ha forestry application of glyphosate. Monkeys tend to have skin absorption rates that are similar to those of humans for most chemicals (Wester and Maibach, 1983), which suggests that a person directly in the path of a herbicide spray with no protection would absorb less than 1% over 12 hours if there was no effort to wash the skin.

The ability of glyphosate to cross the human skin barrier has been studied with *in vitro* techniques by Wester et al (1991). In one approach, sections of the outer layer of skin (stratum corneum) from callus removed in foot surgery were pulverized while frozen. The powder was then mixed with solutions of radiolabeled glyphosate. Glyphosate alone and in formulation (Roundup®) did not move out of solution to bind to powdered stratum corneum, which was the expected outcome because of the limited fat solubility of glyphosate. Chemicals with greater fat solubility will do so. This model is useful for predicting transport through human skin because absorption across skin depends largely on the solubility of the chemical in the fats of the skin.

In diffusion chamber experiments described in the same paper, various dilutions of technical glyphosate and Roundup® formulation were separated from human plasma by an isolated section of whole skin. The transfer of glyphosate to plasma was then measured. Maximum transfer was about 2% over 16 hours, which is consistent with observations of monkeys, and with field observations of applicators (Cowell and Steinmetz, 1990; Lavy et al, 1992)

Glyphosate is not altered in the body; virtually all glyphosate absorbed into the circulation is excreted unchanged by the kidneys in a few days. Following treatment for extended periods, small concentrations of glyphosate can be found briefly in tissues that have the most extensive blood supply, such as the kidney and liver. This behaviour is typical of water-soluble substances. Measurements of urine levels following suicide attempts with massive doses of Roundup® indicate rapid excretion by humans.

Glyphosate was not detectable in eggs, milk or meat after treatment of livestock and chickens with glyphosate in the diet at concentrations up to 75 ppm for 30 days. Work with rats by Brewster et al (1991) has confirmed earlier research that showed rapid excretion of glyphosate without change. After administering radiolabeled glyphosate in a single oral dose of 10 mg/kg of body weights, about one percent of the dose remained in tissues 7 days after administration. The entire label associated with tissues was found to be parent compound. There was an apparent tendency for slower release from bone, possibly associated with some uptake by bone as glyphosate moved from other tissues, but clearance from the body was essentially complete.

To clarify the role of bone as a sink for glyphosate or some portion of the molecule, single doses of 1150 mg of labelled glyphosate/kg were administered intraperitoneally to male and female rats. Sequential blood and bone marrow samples were collected. At 30 minutes after administration 0.0044% of activity was in the bone marrow of males and 0.0072% in the marrow of females. The plasma half times for both sexes were about one hour. The half-time for the decrease of activity in bone marrow was 7.6 hours for males and 4.2 hours in females, leading USEPA to conclude that very little glyphosate finds its way to bone and it is eliminated rapidly (USEPA, 1993).

Although the initial product produced from glyphosate by microorganisms in soil is aminomethylphosphonic acid (AMPA), it is not produced by mammals. Traces have been found in metabolism studies, which probably result from microbial metabolism in the digestive tract.

Humans and probably most other mammals would not be exposed to AMPA in soils or plants, but its behaviour and toxicology has been evaluated, nonetheless. Like glyphosate, it is poorly absorbed, and excreted unchanged. Its toxicity is also quite limited.

General Toxicology of Glyphosate

As already noted, the bulk of toxicology data for glyphosate is in registration documents that have been reviewed by regulatory agencies (USEPA, 1993; World Health Org. 1994; Agriculture Canada, expert scientific contractors for other agencies (SERA, 1996) and in two cases (Giesy et al, 2000; Williams et al, 2000) by academic review teams. Several Environmental Impact Statements for various agencies are separately listed at the end of the references.

The toxicity of glyphosate is limited. Acute oral median lethal doses (LD_{50}) in various species of mammals vary between 3500 and 5000 mg/kg. In part the low oral toxicity is due to poor absorption from the digestive tract, because when injected directly into the abdominal space or intravenously the LD_{50} is less than 200 mg/kg. Mice have tolerated dietary concentrations as high as 50,000 ppm for at least 90 days, with only decreased weight as evidence of effect. No response was seen at 10,000 ppm. 50,000 ppm is 5% of the entire diet, and in mice represents an oral exposure on the order of 7500 mg/kg/day. This high intake is not necessarily inconsistent with the stated acute LD_{50} in the range of 3500 to 5000 mg/kg. In an acute toxicity test the material is usually in solution and administered as a single dose by stomach tube to fasted animals. In a feeding study the diet containing the test material is consumed over the entire day, according to the feeding pattern of the animal, with rapid excretion controlling blood levels. In addition, binding to food particles delays absorption, lowering the already small fraction that can cross the intestinal wall. Rats may be somewhat more sensitive, with some increase in lung weight without evidence of cell damage at a dietary concentration of 5,000 ppm (approximately 300 mg/kg/day).

It is customary to combine carcinogenicity assays with evaluation of systemic effects resulting from lifetime exposure. These studies include observations of physical signs of toxicity, food consumption and body weight, alteration of blood constituents, clinical chemistry, urinalysis and pathological examination. Rats fed glyphosate at concentrations in the diet of 0, 2,000, 8,000, and 20,000 ppm for two years were affected only at the highest rate of intake. Females at the highest dose (equivalent to 1183 mg/kg/day) did not gain as much weight as did females at lower doses rates. Males at the highest intake (equivalent to 940 mg/kg/day) were found to have increased frequency of lens abnormalities, increased liver weight and decreased urine pH. No effects were seen at lower doses in either males or females. The oral no-observed-effect level (NOEL) was 362 mg/kg/day for males and 457 mg/kg/day for females. In beagle dogs given up to 500 mg/kg/day orally by capsule for one year there were no detectable systemic effects.

Dermal and Eye Toxicity

Virtually all exposure to herbicides other than deliberate ingestion is on the skin. Any effects of exposure would be manifested as either irritation of the skin itself, or as systemic effects following absorption through the skin. In North America almost all validated incidents of toxicity following Roundup® exposure have been cases of skin or eye irritation (California Dept of Pesticide Regulation, 1996; Williams et al, 2000).

Application of 5000 mg glyphosate/kg body weight to the skin of rabbits, repeated five times a week for three weeks, caused only slight local irritation. General toxicity at that dose was limited to decreased food consumption by males and increased lactic dehydrogenase (LDH) in serum of both males and females. LDH is an enzyme in cells that leaks into blood serum when the cell wall becomes permeable. There was no

effect at a dermal dose of 1000 mg/kg/day. Rabbits have the most permeable skin of the common laboratory animals and are the best model for skin absorption. In a companion assay in rabbits and rats, single applications of Roundup® were applied to the skin and were covered to improve absorption. Exposures equivalent to 5000 mg glyphosate/kg to rabbits and 17,600 mg/kg to rats produced only skin irritation. A solution of 6.4% Roundup, which is about three to five times the usual spray concentration, applied to rabbit skin five times a week for three weeks caused severe local irritation and some general effects due to stress. Lower exposures did not cause systemic effect (effects other than direct reproductive, cancer and genetic toxicity).

An extensive study of the effect of Roundup® formulation on human skin was done by Maibach (1986). Roundup® was compared with a baby shampoo, a dishwashing detergent and an all-purpose cleaner on 364 student volunteers. The shampoo and the herbicide were found to be similar in effect to water, and less irritating than the detergent and the cleaner. Observations were made at the time of application, and then 24 and 48 hours later. A series of repeated applications over three weeks produced similar outcomes. Other observations indicate that concentrations of Roundup® up to 10% do not cause skin irritation or allergic sensitization. Ten percent formulation is equivalent to 4.1% glyphosate and 1.5% surfactant. Five percent Roundup® will cause eye irritation, however.

Reproductive and Developmental Toxicity, Including Birth Defects

Glyphosate has been subjected to several multigeneration reproduction tests. The two most recent studies are described in the USEPA reregistration document for glyphosate (USEPA, 1993). Rats were administered 0, 3, 10, and 30 mg glyphosate/kg/day in the diet over three generations. An increased incidence of tubular dilatation in the kidney was found in males of the second litter of the third generation. In another assay for two generations, rats were given up to 1500 mg glyphosate/kg/day. The highest dose caused digestive disturbance, decreased food consumption and decreased weight of pups. There were no effects at a daily dose of 500 mg/kg and no kidney effects at any dose. The earlier finding of kidney effects at a lower dose rate was considered to be unrelated to treatment.

Glyphosate has been found to produce no birth defects in rabbits given 0, 75, 175 and 350 mg/kg/day or rats given 0, 300, 1000 or 3500 mg/kg/day. The highest dose in rabbits caused severe maternal toxicity but no effects on either does or their offspring at a daily dose of 175 mg/kg. In the rat, the highest dose did produce maternal and foetal toxicity but not birth defects. The NOEL for maternal and developmental toxicity in rats was 1000 mg/kg/day.

A recent report has suggested the full formulation but not glyphosate itself has adverse hormonal effects on isolated cultured mouse tumour cells. There are a number of flaws in the report, but the most important information is the dose response. The no-effect concentration in the medium is hundreds of times greater than can be achieved in an intact animal, even ignoring all of the barriers to transport. Lin and Garry (2000) looked for evidence of pesticide-induced cell proliferation in cultured breast cancer cells. It is possible to differentiate estrogenic from non-estrogenic effects; they concluded that the induction seen with glyphosate and Roundup was not related to estrogenic activity.

Genetic Toxicity (Induction of Mutations)

Glyphosate has been assayed for mutagenicity in a full range of microbial test systems, in

mammalian cell cultures and in fruit flies and intact mammals. No responses have been observed in validated studies. Glyphosate does not interfere with repair of damaged deoxynucleic acid (DNA). Efficient repair of DNA is a very important component of protection against cancer and other genetic effects. Glyphosate is considered by regulatory agencies to have no genetic activity. Four publications have appeared that are claimed to show some kind of genetic toxicity or DNA damage caused by glyphosate or its formulations. Each has serious flaws in methodology and other aspects; no regulatory agency has found these papers useful. They are mentioned here only because they are often brought forward by groups concerned about herbicide use.

Carcinogenic Potential of Glyphosate

Glyphosate has been the subject of several carcinogenicity studies. Some earlier work has been replaced by more recent observations, described in USEPA (1993). In male mice consuming a diet containing 30,000 ppm glyphosate (3% of the total diet) over their lifetime, equivocal evidence was found for nonmalignant tumours of the tubules in the kidney, but they were not significantly different from controls. This concentration represents a dietary exposure of 5400 mg/kg/day. There was no response in females at any dose or in males at lower doses. This work has since been re-appraised and the regulatory conclusion is that no carcinogenic effect occurred.

Male rats were administered daily doses in the diet up to 940 mg/kg and females received up to 1183 mg/kg/day for two years. There were changes in the pattern of pancreatic, liver and thyroid adenomas. (Adenomas are usually non-malignant tumours.) However, the changes were considered not to be treatment related because of lack of statistical significance, lack of dose-response, similarity to historical controls and lack of progression to malignancy.

Direct carcinogenicity tests in animals provide only part of the information needed for a complete evaluation of the ability of a chemical to cause cancer. The demonstration that glyphosate is negative in all mutagenicity assays indicates that it has no ability to interact with genetic material to initiate the cancer process. It causes little cellular toxicity and does not cause other changes that have been associated with promotion of carcinogenic processes that may have already begun. It is excreted rapidly, unchanged, and is not retained in the body. The fact that glyphosate is not changed in the body is important because almost all direct-acting carcinogens are inert as they enter the body and become reactive with genetic material only after being partially metabolized in the process of detoxication. It is one of nature's paradoxes that the reaction sequence that makes chemicals more soluble (detoxified) so they can be excreted may under some circumstances also make small amounts of them more toxic.

All of these factors are considered in judging that glyphosate is not a carcinogen. Regulatory agencies in Canada, the United States and internationally have concluded that glyphosate is not carcinogenic. The USEPA has placed glyphosate in group E, evidence of non-carcinogenicity. (USEPA, 1992; USEPA, 1993)

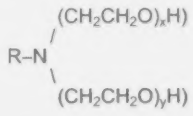
There has arisen a misunderstanding that glyphosate degrades in the environment to formaldehyde, which may be carcinogenic. It does not. The idea arose from use of loose terminology in an otherwise elegant report by Rueppel et al (1977).

Swedish researchers contend that they have found an association between glyphosate use and a form of cancer, but their data do not support the claim.

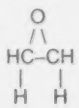
Toxicology and Behaviour of the Surfactant in Vision® Formulation

On a weight basis, 15.4% of the formulation is surfactant and 41% is the active ingredient. The surfactant is a polyethoxylated tallow amine, a type that is also common to cosmetics and household products. There are a multitude of other glyphosate formulations, not all of which are Monsanto products, with many differing concentrations of ingredients. The surfactant decreases the surface tension of water, which causes spray droplets to spread on the waxy surface of leaves, allowing better contact between the herbicide and leaf surfaces. The "skin" of a water droplet is very strong because of the attraction between water molecules (surface tension). The side chains of the surfactant are attractive to water molecules and decrease their ability to adhere to one another. The surfactant may also aid in penetration of the leaf surface.

Monsanto (1992) has published a fact sheet which describes the molecule. The structure is described:



where x + y have an average value of 20. This means that the two side chains (x + y) are of variable length and have an average size, together, of 20 ethylene oxide units, or 40 carbons. Ethylene oxide looks like this:



The R in the surfactant structure represents the tallow, which is really long- chain saturated fatty acids derived from tallow (or lard). Those fatty acids are typically chains of 16 to 20 carbon atoms. Saturation means that there are two hydrogens on each carbon, which is all there is room for. (Vegetable oils are unsaturated, which means that they have less than the maximum number of hydrogens. The carbon chains with fewer hydrogen atoms are more flexible and therefore form a fluid. Carbon chains of lard or tallow are saturated and relatively inflexible.)

The nitrogen (N in the structure above) is added in the manufacturing process, and is the point of attachment of the polyethoxy chains to the tallow. The nitrogen with three linkages is the basis for the term, "amine" in the name of the substance. The average molecular weight of the surfactant should be expected to be about 1100–1200. That of the glyphosate isopropylamine salt is about 228. A lower molecular weight means that there are more molecules of the material per given weight. At 15.4% surfactant and 41% glyphosate IPA, that means that there is only about 1 molecule of surfactant for 13 molecules of glyphosate.

There have been several studies on biological effects of this surfactant and related structures, the oldest of which was reported in a paper on various polyoxyethylene tallow amines by Goater et al (1970), describing work dating to 1962. The acute median lethal oral dose (LD_{50}) was estimated to be 1850 mg/kg, in rats. Somewhat smaller doses for two to ten days resulted in gastrointestinal damage and congestion of vessels in various organs. At dietary concentrations of 4500 ppm (roughly 200 mg/kg/day) over 90 days, rats lost hair and became lethargic. At 1500 ppm weight gain was reduced but other effects were not seen. Dogs given 40 or 120 mg/kg/day over 90 days failed to gain weight normally and were found to have gastrointestinal effects. At 13 mg/kg/day (500 ppm in the diet) there were no effects observed.

A general battery of assays on the specific surfactant of the formulation has been conducted (Monsanto Canada, 1992). The material is irritant to skin and eyes of rabbit and causes some allergic sensitization in guinea pig skin. However, the whole formulation itself has shown no potential for sensitization, and is much less irritating than the undiluted surfactant. Observations of rats and dogs over 90-day

feeding studies indicated responses quite similar to those reported by Goater et al (1970). Gastrointestinal irritation is the primary effect.

The surfactant has been assayed for genetic activity in two systems. In the Ames assay, using four strains of Salmonella, no genetic effect could be found, and a bone marrow assay for chromosome damage in mice was also negative. In testing for developmental injury, no malformations were found even at doses that caused significant maternal toxicity.

Toxicology of the Vision® Formulation

A number of studies have been conducted on the effects of the formulation Roundup®, which is identical to Vision®, except that at the time the work was done, levels of the contaminant 1,4-dioxane were on the order of 300 parts per million, as reported by Monsanto in 1980. It was determined by USEPA at that time that risks associated with 1,4-dioxane at that level would be negligible. 1,4-dioxane arises in the synthesis of the surfactant, but is no longer detectable in the formulation (Monsanto Canada, Inc, 1991).

Acute toxicity of undiluted Roundup® is similar to that of glyphosate alone. The median lethal doses (LD_{50}s) are on the order of 4000-5000 mg/kg. Goats tolerated doses of 1000 mg/kg with no signs of toxicity. Such a dose is 10 to 20 times the intake that would occur with a day of feeding on directly sprayed grass. Dermal application of 17,600 mg/kg to rats resulted in no abnormal behaviour. Over longer periods of dermal exposure of rabbits (21 days) to various concentrations of Roundup®, evidence of systemic effects appeared but were secondary to stress associated with skin irritation.

Undiluted Roundup® is moderately irritating to rabbit skin and eyes. The effects are reversible within a few days. A spray mix dilution of 5% Roundup® is slightly irritant and quickly reversible. Guinea pig sensitization tests were negative. Acquavella et al (1999) evaluated 1513 calls to a regional Poison Control Centre made over a five year period, to appraise the extent and persistence of ocular injury. About 90% of the cases involved minor, transient or no symptoms. There was temporary injury in two percent of cases. There were no instances of permanent change.

The registrant has conducted sequential insult patch tests with Roundup® on volunteers at dilutions of 2.2% (the intended concentration for application) and 11.1%, and found that these levels are not primarily irritant to skin, nor was the solution a sensitizing agent.

Although inhalation exposure is not significant for applicators, subchronic inhalation assays have been run. Thirty-day exposure of rats to an aerosol containing one part Roundup® and two parts water at a concentration of 360 mg glyphosate/cubic metre) caused minor nasal irritation but no other effects. Rats were also exposed for six hours daily, five days per week for three months to concentrations of 1000 and 5000 mg Roundup®/cubic metre of air. Such concentrations are not possible in any field situation, even for a short period. There were no effects on survival, growth, behaviour, blood constituents, and urine or tissue pathology. Liver and lung weights were depressed compared to controls, but there was no tissue or cellular abnormalities in those organs.

Martinez and Brown (1991) reported significant lung damage following direct instillation of a 7% solution of the surfactant into the trachea of anesthetized rats. The effect was compared with that of a solution of polysorbate-20, another anionic surfactant, which produced less injury. This information relates to the pulmonary injury resulting from inhaling vomitus after a suicide attempt and has little practical relevance to worker health questions. The doses were 0.1, 0.2 and 0.4 ml of seven percent surfactant to 350 g rats, which is equivalent to placing 7.5, 15 and 30 ml of concentrated Vision® directly into the trachea of a 50 kg adult human. This would also be equivalent to aspirating a mouthful of concentrated herbicide into the lung. The reflex

coughing that occurs when one mistakenly allows even a minute amount of water into the trachea indicates the difficulty of inhaling the herbicide as a liquid.

Exposure Studies

Absorption of glyphosate during backpack application is minimal. Cowell and Steinmetz (1990) measured exposures of workers applying glyphosate formulation in Southern pine reforestation programs, using biological (urine) and patch monitoring, hand washing and breathing zone sampling. They collected urine for three days following the application day, a time period that accounted for virtually all of any glyphosate that was absorbed. On the day of application glyphosate was evident in urine of only five of the 16 workers in the study. No measurable residues were detected thereafter.

Three of the workers mixed the herbicide in preparation for application as well as applying it. As is customary in reporting such data, negative samples were assumed to contain half the minimum detection limit. In other words, if the lowest detectable amount was 0.00001 mg/ml (0.01 ug/ml), a negative sample was assumed to contain 0.000005 mg/ml. On that basis, the cumulative collections per person ranged between 0.012 and 0.030 mg. Doses per hour were calculated to be between 0.000017 and 0.000078 mg/kg. Most were between 0.00002 and 0.00004 mg/kg/hr. If the highest dose is used for risk estimation, the daily dose would be about 0.0006 mg/kg.

The passive estimation of dosage on the basis of surface contact and breathing zone measurements indicated higher exposures than direct determination of urinary excretion by about an order of magnitude. The breathing zone samples indicated respiratory exposure (not dose) 2-3 times the amounts found in the urine. Because urinary excretion is known to represent the entire absorbed dose, the amounts found in inhaled air indicate that absorption from the lungs and air passages is inefficient, as was already known for the skin and digestive tract. Doses estimated from amounts found on patches on and under clothing, and in hand washes, using absorption rates from experimental absorption studies, were roughly ten-fold higher than the direct measurement indicated.

A study of forest nursery workers also showed that exposure was very low (Lavy et al, 1992). However, most of the workers applied glyphosate to individual weeds with a conical device that prevented movement to adjacent nursery stock, a method that also diminishes worker exposure. Average doses per hour of herbicide use were 0.000039 mg/kg for ground applicators with hand-held tools, and 0.000065 mg/kg for three operators of tractor mounted sprayers. The work included as many as nine applications over an 88-day period. As was the case in the work by Cowell and Steinmetz (1990) data from passive dosimetry indicated more than a ten-fold greater exposure than did the actual measurement of absorbed material. While this kind of application has little relevance to most silvicultural vegetation management, it does illustrate the limited movement of glyphosate across the skin, and again shows the error inherent in using cloth patch methods for dose estimation.

Using either set of figures, the exposures and doses acquired by workers were very low, and suggest that in the field absorption is much lower than the two or three percent indicated in laboratory studies designed to maximize movement into the circulation. In part, this difference may result from adsorption and binding of glyphosate to soil and other foreign material that will inevitably be on the skin when working in the field. Absorption of the Roundup® formulation also appears to be much lower than absorption of some other herbicides.

In Finland, one method of vegetation clearing is with brush saws equipped with a pressurized herbicide sprayer. In a study of five operators of this equipment spraying Roundup®, breathing zone and urine glyphosate measurements were made. (Jauhiainen et al, 1991) The mix used was 8% Roundup®, 87% water, and 5% of an

unspecified "carrier liquid." Air concentrations were very low, usually less than the detection limit of 1.25 microgram per cubic meter. This would translate to an inhaled dose of less than 0.00015 milligrams per kg per workday. Two samples were found to contain 2.8 and 15.7 micrograms per cubic meter, which are still trivial levels. Urine concentrations were undetectable in almost every case, which again suggests that breathing zone concentrations do not translate well to absorbed dose. Clinical examination provided no evidence of health effect.

The limited exposure by inhalation is consistent with numerous studies with other pesticides, even with such equipment as mist blowers. (Lavy et al, 1980; Nigg and Stamper, 1983; Libich et al, 1984; Abbott et al, 1987)

The workers observed by Jauhiainen et al (1991) almost certainly had extensive contact with the treated vegetation before the herbicide has dried, with considerable opportunity for dermal absorption. The workers observed by Cowell and Steinmetz (1990) also probably had some contact with treated vegetation before it dried. The near absence of glyphosate from urine indicates that such exposure is not likely to result in significant systemic doses. These findings are also consistent with the exposure studies discussed above. The study, though small, is also of some value in examination of health effects of saw emissions, since considerable clinical data was gathered from these subjects.

A worst case estimate of total dose in a direct exposure to a spray can be made on the basis of skin exposure information. An application of 2 kg/ha on a person with 20% of body surface uncovered (about 4000 square centimetres; no hat, short sleeves, exposed lower legs) would deposit a total of 80 mg or 0.020 mg/square centimetre to a surface from which it could be absorbed. If 1% is absorbed the total dose would be about 0.8 mg or 0.016 mg/kg for a 50 kg person. As will be shown in the risk assessment below, this dose is toxicologically inconsequential.

Combustion of glyphosate and potential exposures to combustion products is discussed in the paper on exposure. Even with worst case assumptions neither glyphosate itself nor its products of combustion, all of which are chemicals commonly encountered in industry, will reach concentrations that are more than a small fraction of allowable workplace standards.

Suicide Attempts

While suicide attempts have nothing to do with occupational or public exposure to a herbicide, there has been publicity about suicides with the Roundup® formulation, which should be discussed in this report.

Beginning in the eighties, in some parts of Asia, Roundup® formulation was used in a number of suicide attempts, some of which were successful. Almost all of the reports have come from Japan or Taiwan (Sawada et al, 1988; Talbot et al, 1991; Tominack et al, 1991) Identity as a "weed killer" may have caused some to think the formulation would also be lethal to humans, but other herbicides have apparently not been used. Also the very high comparative toxicity of insecticides seems not to have led to unusual frequency of their use. The reason may be a rather bizarre factor that has recently come to light. Along with the mistaken idea that a weed-killer is likely to be lethal to humans, the formulation is more expensive than most, which may be believed to confer some sort of status.

There is useful information in the reports on the suicide victims. The first English language report of Roundup® suicide attempts was a letter to the medical journal Lancet by Sawada et al (1988) which was based on an earlier report published in Japanese. Other large series of cases have been described. Tominack et al (1991) discussed 97 cases recorded between January 1986 and September 1988 at the Taiwan National Poison Centre, of which 11 were fatal.

Talbot et al (1991) reviewed 93 cases seen at the Changhua Christian Hospital in Taiwan between 1980 and 1989. Seven of these patients died. Chang et al (1999) reported on 50 deliberate ingestions and Lee et al (2000) evaluated medical charts of 131 suicide attempts in Southern Taiwan to identify characteristics that would aid in prognosis and treatment. A few other cases have also been reported independently.

In suicide or attempted suicide cases, only approximations of the doses ingested can be made. Fatal cases were estimated by Talbot et al (1991) to have ingested 85-200 ml, but survival of a 500-ml dose was reported. Tominack et al (1991) estimated fatal doses to average 263 ml (8-9 oz). The three reports can be summarized as showing injury that should be expected of surfactant or detergent damage to the gastro-intestinal tract, followed by various secondary responses to the extensive tissue damage. There is some evidence to suggest that at such high doses some surfactant can be absorbed from the damaged intestinal wall to be transported to the lung, where it causes leakage of fluid from fine blood vessels. All of the cases described were suicide attempts and bear no relation to occupational or environmental exposures.

The average estimated ingested dose of formulation reported by Tominack et al (1991) (above) represents about 2100 mg of glyphosate/kg and about 780 mg of surfactant/kg, for a 50 kg (110) lb) person. These amounts may be compared with the very low doses likely to be acquired by applicators, discussed below.

Assessment of Risks to Workers Who Apply Vision or Who Enter Treated Areas

Glyphosate is not carcinogenic or mutagenic. It does not cause reproductive or foetal effects other than at doses that directly intoxicate the mother. Studies of the whole formulation and of the surfactant separately indicate that mammalian toxicity of the formulation is of the same order as that of glyphosate itself. The surfactant is negative in Ames bacterial mutagenicity tests and in a mouse bone marrow assay for chromosomal damage. It does not cause foetal effects at doses high enough to cause maternal toxicity. Because there is no evidence of genetic or reproductive toxicity, a quantitative assessment of such risks associated with use of glyphosate formulations is not possible.

Absorbed doses resulting from exposure to glyphosate under operational conditions have been shown to be very low, primarily because absorption through the skin is difficult, even when substantial amounts are deposited. As a basis for estimation of risk of systemic toxicity, the maximum daily intake estimated by Cowell and Steinmetz (1990) for backpack applicators, 0.0006 mg/kg/day is used. The dose to most applicators was less than half that amount. The systemic oral no-observed-effect level (NOEL) established by US EPA for glyphosate is 175 mg/kg (USEPA, 1993; USEPA, 1998). The rate of absorption in animals at low doses is about 15% and may be less. The margin of safety, or difference between (NOEL x 0.15) and absorbed occupational dose would be 26.25/0.0006 = about 44,000. A hypothetical case may be set up for a poorly clothed 50-kg person directly sprayed on 20% of body surface at a rate of 2 kg/ha. If 1% skin absorption is assumed, the dose is 0.016 mg/kg or 0.032 mg/kg if absorption is 2%. The margin of safety in the latter case would be 26.25/0.032 = about 800.

The only adverse response that may be expected in use of Vision® is skin irritation should the concentrated formulation come in contact with the skin. Immediate washing will almost certainly prevent such an effect. The formulation diluted for application may cause irritation if splashed in the eyes. Such exposure will not result in allergic sensitization.

Conclusion

The toxicity of glyphosate and its formulations is extremely limited. Glyphosate is not carcinogenic, it does not produce reproductive or genetic effects, and doses required to produce non-specific systemic effects are very high. Workers applying glyphosate or occupying areas recently treated have been shown to absorb only small amounts of the herbicide, that have no toxicological significance. Glyphosate binds tightly to vegetation and soil, and does not move through the soil from the site of application. Exposure by dislodgement from vegetation is unlikely. Ingestion of the concentrated formulation can be expected to cause gastrointestinal effects, and exposure of skin or eyes to the concentrate may result in irritation if it is not washed away.

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Glossary

Acute toxicity – (Short term toxicity) –Acute toxicity is the quality or potential of a substance to cause injury or illness from a single dose or short period of exposure. See **subacute, subchronic and chronic.**

Adjuvant – Any additive to a pesticide formulation that is not active itself, but is intended make the active ingredient work better.

Cancer – A malignant growth of potentially unlimited size that invades local tissues, and may spread to other parts of the body.

Carcinogen – A chemical capable of inducing cancer.

Carcinogenic – Capable of causing cancer.

Chronic toxicity – (Long-term toxicity)- Chronic toxicity is the quality or potential of A substance to cause injury or illness after repeated exposure for a long period of time. Chronic toxicity tests run for a year or more; for rodents the period may extend through the entire life span. A chronic effect persists for months or years and may arise from acute or long term exposure. See **acute, subacute, subchronic.**

Contaminant – In a formulation, usually residues or impurities from the manufacturing process present in small quantities. Contaminants must be identified to the regulatory agency, which judges whether they are of concern.

Deoxyribonucleic Acid – See **DNA.**

Degradation – Breakdown of a compound by physical, chemical or biochemical processes into basic components with properties different from those of the original compound.

Detection limit – The lowest concentration of a chemical that can be identified in a substance (e.g., soil, foliage or body fluids). Analytical sensitivity varies among chemicals, and in different media. The detection limit is usually lower than the level that can be reliably measured. For example, it may be possible to find a substance present at 0.01 parts per billion, but only at levels above 0.03 ppb can the amount be stated.

Detoxication (Detoxification) – The biochemical process of changing a chemical in the body to a less toxic form or to a form that can be more easily excreted.

Dose – The amount of a chemical that actually enters the body to be distributed to all of the organs and cells. Distribution to tissues and cells is selective, and depends on the nature of the chemical and characteristics of each kind of cell.

Dose-response relationship – The central idea in toxicology and in pharmacology (which is the science dealing with beneficial effects of therapeutic drugs). As the dose (or concentration) of a chemical increases, the effect increases, and as the dose is lowered, the effect becomes less. This response pattern applies to every interaction between a chemical and a biological system, whether human, fish, bacteria or any other kind of organism or tissue. The dose-response relationship is absolutely essential to judgement of the effect of any chemical.

DNA (Deoxyribonucleic Acid) – The genetic library in each cell that contains all of the instructions for building and operating the body. Each kind of cell contains all of the information for the whole body. Only the information needed for each kind of cell is used by that cell; the rest is repressed. Liver cells do not try to be muscles, and muscles do not try to become brain cells, but they contain all of the information.

Epidemiology – The scientific study of the cause, distribution, and control of epidemics or other disease in a region. In the context of these reports, epidemiology is the study of possible associations between environmental and occupational chemicals and occurrence of diseases. The term "associations" is used in its statistical sense, which means that the relationship cannot demonstrate cause and effect.

Exposure – Amount of a chemical that reaches a surface from which it might be absorbed. The dose is some fraction of the exposure. Exposure does not include material that is on nearby foliage or other surfaces. It is only the material that reaches the skin (by contact), respiratory tract (by inhalation) or digestive tract (by ingestion).

Foetus – The later stage of mammalian development in the womb. In human, this refers to the unborn child during the period of uterine life from the end of the second month until birth.

Foetal toxicity – Direct effects of a toxicant on the foetus, independent of effects on the mother.

Formulation – A complete pesticide preparation as sold by a manufacturer for practical use. It includes the active ingredient and any necessary adjuvants and solvents. For use, it may or may not require further dilution or mixing with other substances. Formulation can also be defined as the process used by manufacturers in preparing a pesticide for practical use.

Half-life – The length of time required for disappearance of half of the material present in an organism or in environmental media. It is a more useful idea than "persistence" because it allows prediction of the time required to reach low target levels with out making measurements over exceedingly long periods. A better term is "Half-time," because the information only relates to a given location, and says nothing about the processes that deplete the chemical. If it evaporates or is carried away intact by water it may still exist in its original form. The term "half-life" originated with description of radioactive decay, in which elements become a totally different substance. The English language sometimes loses precision as it evolves.

Herbicide – A chemical substance or cultured biological organism, used to kill or suppress the growth of plants.

Immune system – All of the structures and cells and their products that protect against infectious organisms and against cells of the body that have become altered in the very early development of cancer.

Inert ingredient – Any component of a formulation that is purposely added and does not have pesticidal activity. Includes solvents and adjuvants, not manufacturing impurities.

Irritation – A purely local or topical reaction which may include redness, blistering, swelling, burning or itching.

LD_{50} – Acronymn for Median lethal dose.

Lethal – Causing death.

Lethal concentration (LC_{50}) – Rate at which 50 percent of test animals will be killed.

LOAEL – Acronym for lowest-observed-adverse-effect level.

Lowest-observed-adverse-effect level (LOAEL) – The lowest measured amount of a chemical that produces significant increases in frequency or severity of adverse effects in exposed subjects. in the general sense it includes all biochemical, pathological, behavioral, reproductive, genetic and other measurable changes. the term may also be applied to any specific parameter under observation.

Malignant – Deadly or very injurious. As applied to cancer, invasive of local tissues and metastatic (migration of cancer cells to other tissues).

Margin of Safety (MOS) – The difference between the estimated dose of a pesticide and the NOAEL. A **MOS** of 100 (estimated dose 100 fold less than the NOAEL) is usually considered to assure that no adverse effects will occur.

Median lethal dose (LD_{50}) – The dose of a chemical, biological agent, or other substances that causes death in 50% of defined test animals.

Metabolism – the sum total of the biochemical reactions that a chemical undergoes in an organism. The processes include biochemical (enzymatic) reactions in the cells of the body that convert nutrients to energy and structural materials of the body; reactions that change wastes so they can be removed; and reactions that convert foreign substances, such as some pesticides to forms that can be excreted.

MOS – Acronym for margin of safety.

Mutagenic – Capable of producing genetic changes.

Mutagens – Chemicals that are able to induce gene or chromosome damage that is stable and survives cell division to reach the next generation of cells. See **mutation.**

Mutation – Genetic change in DNA of a cell that can be transmitted to the next generation of cells. If in sperm or egg cells, a mutation may be transmitted to offspring. If in somatic (body) cells such as liver, muscle or other organs, a mutation may pass to daughter cells in the organ. The change may have no effect on cell function or it may damage the cell, or even imaginably improve it.

NOAEL – Acronym for **no-observed-adverse-effect level.**

No-observed-adverse-effect level (NOAEL) – The dose rate or concentration at and below which no adverse effects can be detected. (See **threshold; SEE LOAEL)** If the estimated dose of a herbicide to a worker is very low compared to the **NOAEL** for the most sensitive effect found in the laboratory, no harmful effect is to be expected.

NOEL – Acronymn for **no-observed-effect level.**

No-observed-effect-level – (NOEL)-Dose of a chemical or biological agent at which there are no biologically or statistically significant effects attributable to treatment. The term can refer to adverse, beneficial or meaningless effects and is falling out of use in toxicology.

Persistence – The duration of measurable concentrations of a pesticide in soil, foliage or other media. (See Half-life.)

Pesticide – Any chemical (or biological product) intended to control or kill pests. Herbicides, insecticides, fungicides are all pesticides. The term is sometimes incorrectly used to mean only insecticide, for example "pesticides and herbicides."

Registration – The process by which government (e.g., Canadian federal government) authorities determine that a pesticide is suitable for use. Standards of public and worker safety, environmental impact, and usefulness must all be met.

Risk – The probability (likelihood) that some adverse or undesirable effect will take place in the future, as a result of some specified activity. Risk may relate to health, finances or any other kind of undesirable impact. Real risk may be so small that it cannot be distinguished from zero, or so great that it is a certainty. In the context of pesticides, risk is the probability that use of the pesticide will result in some specified harmful effect on workers or the public. Risk assessment is the process of estimating that probability.

Safety Factor – See **Margin of Safety.**

Sensitization – The initial exposure of an organism to specific antigen (foreign protein or chemically altered body protein) resulting in a response of the immune system such that subsequent exposure induces an allergic reaction.

Subacute – Extending over a few days to perhaps a month. This and related terms do not carry defined time periods; consequently there is overlap in the way they are used. See **Acute, subchronic and chronic.**

Subchronic – For experimental studies, relatively long term, but not as long as a chronic study. Typically three to six months. See **acute, subacute, and chronic.**

Teratogen – A chemical that can cause birth defects.

Teratogenic – Relating to or able to produce birth defects.

Threshold – The lowest dose that will produce a given effect. As a practical matter, the threshold is little different from the **NOAEL.**

Tolerance – Lesser than normal sensitivity of an individual to the adverse effect of a chemical. also, the allowable residue of a pesticide on a food or feed crop.

Toxicant – A toxic agent; a poison.

Toxicity – The whole pattern of harmful effects (illness and other undesirable effects) that a chemical can cause. It is a property of the chemical; it does not change.

Toxicology – The group of scientific disciplines that identifies and studies the adverse effects of chemicals on biological systems, whether in the laboratory or in the field.

Toxin – A poisonous substance produced by a living organism. The term is sometimes incorrectly used in reference to non-biological chemicals.

Tumour – a new growth of cells multiplying progressively and without control. Classically, the term means a swelling.

Titles in this Series

1 Principles of health effects evaluation and risk estimation for chemicals that may be encountered in forest vegetation management

2 Pesticide testing for registration: toxicity, environmental behaviour, and epidemiology

3 Toxicology and potential health risk of chemicals hat may be encountered by workers using forest vegetation management options. Part I: Risk to workers associated with exposure to emissions from power saws

4 Toxicology and potential health risk of chemicals that may be encountered by workers using forest vegetation management options. Part II: Exposure to and absorption of herbicides used in forestry

5 Toxicology and potential health risk of chemicals that may be encountered by workers using forest vegetation management options. Part III: Risk to workers using 2,4-D formulations

6 Toxicology and potential health risk of chemicals that may be encountered by workers using forest vegetation management options. Part IV: Risk to workers using glyphosate formulations (e.g., Vision®, Roundup®, Vantage Forestry® and Forza®)

7 Toxicology and potential health risk of chemicals that may be encountered by workers using forest vegetation management options. Part V: Risk to workers using hexazinone formulations (Pronone®, Velpar® L)

8 Toxicology and potential health risk of chemicals that may be encountered by forest vegetation management workers. Part VI: Risk to workers using triclopyr formulations (Release®, or Garlon 4®)

9 Toxicology and potential health risk of chemicals that may be encountered by workers using forest vegetation management options: Summary

Title Number

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